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One-pot synthesis of functionalized β-amino sulfides/β-amino selenides *via* ring opening of cyclic sulfamidates

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Abstract: A number of functionalized β-amino and γ-amino sulfides and selenides have been synthesized involving a one-pot process of ring opening of cyclic sulfamidates with '*in situ*' generated thiolate and selenoate species from diaryl disulfides and diphenyl diselenide using rongalite. A mild and efficient method has been developed for the synthesis of cysteines from serine.

Introduction

Compounds containing sulfur/selenium and nitrogen have generated profound interest due to their applications in drug design,[1, 2] organo catalysis,[3-9] and medicine[10-12] etc. Among these compounds, β-amino sulfides have recently received much attention. For example, some of these compounds serve as potent inhibitors of various toxins like tetanus toxin,[13] and botulinum neurotoxin type B.[14] On the other hand, organoselenium chemistry plays a pivotal role in the synthesis of a large number of biologically active compounds and they are important in therapeutics.[15] Recent advances in the synthesis of organoselenium compounds have been propelled by the interesting reactivities[16] and their potential pharmaceutical significance.[17] Moreover, β-amino sulfides/selenides are used as excellent chiral ligands in asymmetric catalysis and hetero bidentate N,S-ligands have proved to be very effective in enantioselective palladium-catalyzed allylic substitution reactions.[4-9] In general the synthesis of β-amino sulfides/selenides has been achieved using the the ring opening of aziridines,[18-20] and nucleophilic substitution of amino alcohols derived tosylates by thiolate/insitu generated selenoate anion.[21, 22] From our laboratory, we have earlier reported the synthesis of the β-amino sulfides/selenides by ring opening of aziridines by chalocgenide anions generated *in situ* from-

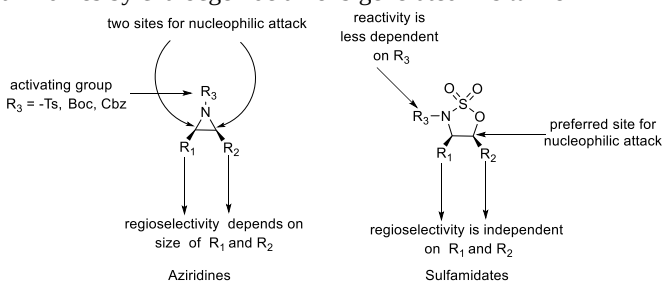
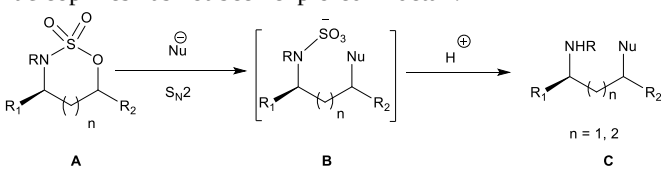


Figure 1. Reactivity of aziridines *vs* cyclic sulfamidates

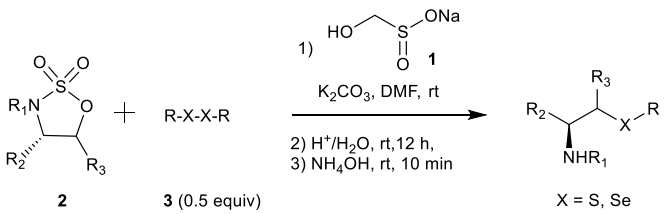
dichalcogenides mediated by rongalite (**1,** Sodium hydroxymethanesulfinate).[19]

However the regioselectivity of ring opening in the case of highly substituted aziridines is a serious problem. The size of substituents $\mathbf{R_1}$ and $\mathbf{R_2}$ and the nature of protecting group $\mathbf{R_3}$ on nitrogen atom dictate the course of the reaction (Figure 1). To overcome these problems, we decided to study the reactivity of cyclic sulfamidates with organic disulfides in the presence of rongalite **1**.

Cyclic sulfamidates are considered as synthetically versatile electrophiles that can be synthesized from readily available (and enantiomerically pure) 1,2- and 1,3-amino alcohols or 1,3-diols.[23] Ring opening reactions of cyclic sulfamidates **A** with nucleophiles can give *N*-sulfate intermediate **B**, which on further hydrolysis with either protic or Lewis acidic conditions results in the formation of the final product **C** (Scheme 1).[24] However, the ring opening of cyclic sulfamidates with sulfur nucleophiles has not been explored in detail.[25]



Scheme 1. Nucleophilic ring opening of sulfamidates



Scheme 2: General scheme for the synthesis of β-amino sulfides/selenides

We have already reported the synthesis of β-amino disulfides/diselenides from aziridines[26] and sulfamidates[27, 28]

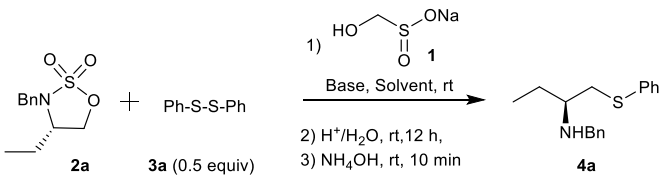
using benzyltriethylammonium tetrathiomolybdate $[BnEt_3N]_2MoS_4$ as a sulfur transfer reagent.

Herein, we wish to report the synthesis of β-amino sulfides/selenides *via* ring opening of cyclic sulfamidates using diaryl dichalcogenides in the presence of rongalite **1** (Scheme 2).

Results and discussion

Reaction of sulfamidate 2a with diaryl disulfides 3 in the presence of rongalite 1

Initially, the sulfamidate **2a**[28] derived from (*S*)-2-amino butanol **2a** was taken as a model substrate for screening (Scheme 3).



Scheme 3. Reaction of sulfamidate **2a** with diphenyl disulfide **3a** in the presence of **1**

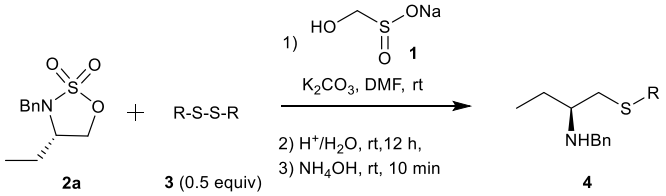
Table 1. Optimization of reaction conditions for the formation of **4a**.

Entry	Conditions			Yield (%)[b]
	Base (1.5 equiv)	Solvent	Time (h)[a]	
1	–	DCM	8	–
2	K_2CO_3	DCM	3	10
3	K_2CO_3	CH_3CN	3	35
4	K_2CO_3	THF	3	52
5	**K_2CO_3**	**DMF**	**1**	**86**
6	Et_3N	DMF	1	78
7	$CSCO_3$	DMF	1	82

[a]Time required for the reaction of sulfamidate **2a** with disulfide **3a** in the presence of rongalite **1.**

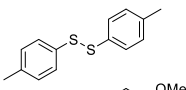
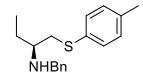
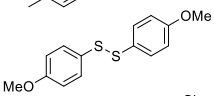
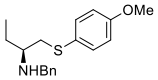
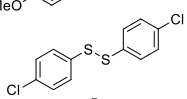
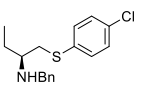
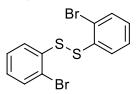
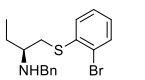
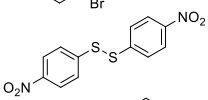
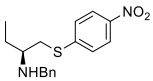
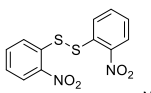
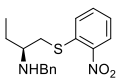
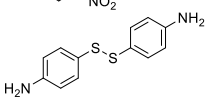
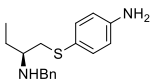
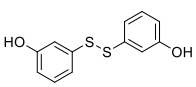
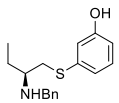
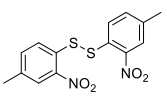
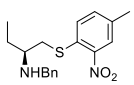
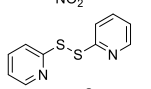
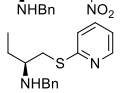
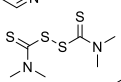
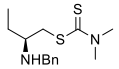
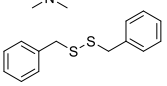
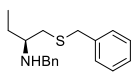
The ring opening of sulfamidate **2a** by the thiolate ion formed by the cleavage of diphenyl disulfide **3a** by rongalite **1** was studied in different solvents and bases and the results are presented in table 1. Screening revealed that the reaction gave the best yield when the reaction was performed using K_2CO_3 as a base and DMF as the solvent (Table 1, entry 5).[29] It was observed that the product **4a** was not formed in the absence of a base (Table 1, entry 1). The mechanism of the reaction as proposed previously[19, 30, 31] involves the base promoted decomposition of rongalite to form formaldehyde and HSO_2^-. The HSO_2^- transfers a single electron to disulfide **3a** to form a thiolate ion *in situ* which reacts at the C-O bond of **2a** in a highly stereospecific manner (S_N2). After the reaction is over, the reaction mixture is acidified, stirred overnight followed by neutralization with aqueous NH_3 to furnish the corresponding β-amino sulfide **4a**.

Having optimized the conditions, we next explored the scope and generality of the method with various aryl/alkyl disulfides (Scheme 4).



Scheme 4. Ring opening of (*S*)-2-amino butanol derived sulfamidate **2a** with various disulfides **3**

Table 2. Synthesis of β-amino sulfides **4** derived from sulfamidate **2a** and disulfides **3**

Entry	R-S-S-R		Time (h)[a]	Product		Yield (%)[b]
1		**3b**	0.75		**4b**	93
2		**3c**	1		**4c**	95
3		**3d**	1.5		**4d**	90
4		**3e**	1.5		**4e**	93
5		**3f**	2		**4f**	87
6		**3g**	2		**4g**	85
7		**3h**	1.5		**4h**	89
8		**3i**	1.5		**4i**	89
9		**3j**	1.5		**4j**	85
10		**3k**	1		**4k**	82
11		**3l**	1		**4l**	95
12		**3m**	6		**4m**	No reaction

[a]Time required for the reaction of sulfamidate **2a** with disulfides **3** in the presence of rongalite **1**.
[b]Isolated yields after purification by column chromatography.

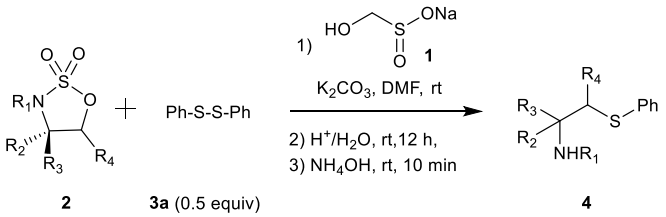
We have been able to synthesize the corresponding substituted and enantiopure β-amino sulfides **4** by employing the route outlined in scheme 4 and the results are summarized in table 2. Irrespective of the nature of the functional group on the phenyl ring of the disulfide, the corresponding β-amino sulfides were obtained regioselectively in good to excellent yields (Table 2, entries 1–9). Heteroaryl disulfide such as 2,2'-dipyridyl

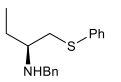
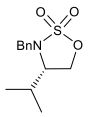
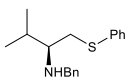
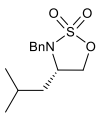
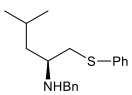
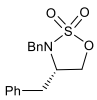
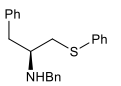
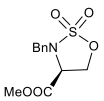
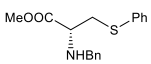
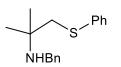
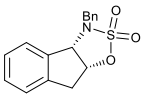
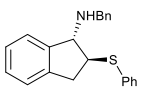
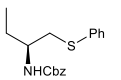
disulfide **3k** reacted reasonably well with the sulfamidate **2a** in the presence of **1** to furnish the corresponding β-amino sulfide **4k** in 82% yield (Table 2, entry 10). Additionally, aliphatic disulfide like tetramethylthiuram disulfide **3l** also gave the corresponding β-amino sulfide **4l** in excellent yield (95%) (Table 2, entry 11). However dibenzyl disulfide **3m** failed to react under these conditions (Table 2, entry 12).

Reaction of various sulfamidates 2 with 3a in the presence of 1

We further extended the methodology to various sulfamidates[28] (**2a–2h**) using diphenyl disulfide **3a** as the reaction partner. The results are presented in table 3.

Table 3. Synthesis of β-amino sulfides **4** from various sulfamidates **2a–h** and diphenyl disulfide **3a**



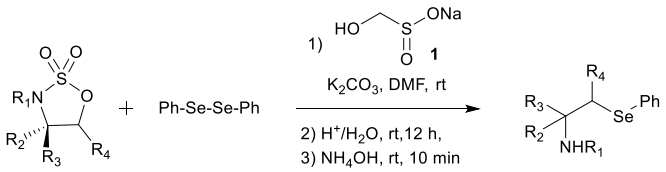
Entry	Sulfamidates		Time (h)[a]	Product		Yield[b] (%)
1		**2a**	1		**4a**	93
2		**2b**	1		**4n**	95
3		**2c**	1		**4o**	94
4		**2d**	1		**4p**	92
5		**2e**	1		**4q**	82
6		**2f**	2		**4r**	80
7		**2g**	3		**4s**	82
8		**2h**	1		**4t**	84

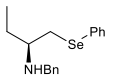
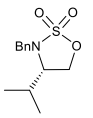
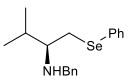
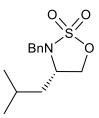
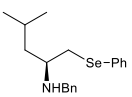
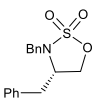
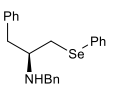
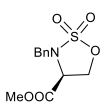
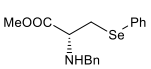
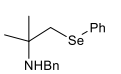
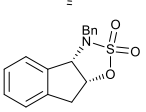
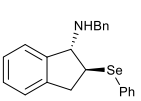
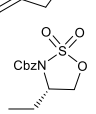
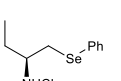
[a]Time required for the reaction of sulfamidates **2** with disulfide **3a** in the presence of rongalite **1**.
[b]Isolated yields after purification by column chromatography.

The sulfamidates **2b–2e** derived from valine, leucine, phenyl alanine and serine gave the desired products **4n–4q** respectively in excellent yields (Table 2, entries 2–4). However, substituted sulfamidates such as **2f** derived from 2-amino-2-methyl-1-propanol, and **2g** derived from (1*S*, 2*R*)-1-amino-2,3-dihydro-1H-indan-2-ol reacted slowly (2–3 h) with phenyl thiolate anion generated *in situ* from diphenyl disulfide **3a** and rongalite **1** to furnish the corresponding β-amino sulfides **4r** and **4s** in good yields (Table **2**, entries 6,7). This may be due to steric effect of the groups present at the α and β carbon atoms. Protected (Cbz) sulfamidate **2h** derived from 2-amino butanol also reacted smoothly to furnish the desired product **4t** in 84% yield (Table 2, entry 8). These results suggest that the reaction is general and it overcomes all the problems encountered in the case of aziridines in term of product formation and selectivity.

Reaction of various sulfamidates 2 with diphenyl diselenide 3n in the presence of 1

Table 4. Synthesis of β-amino selenides from various sulfamidates **2a–h** and diphenyl diselenide **3n** in the presence of **1**



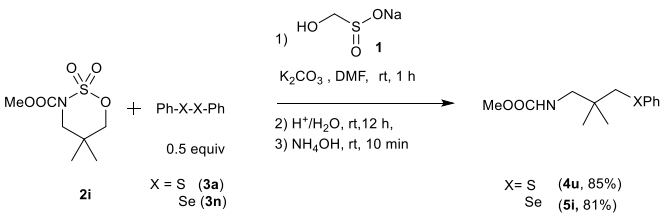
Entry	Sulfamidates		Time (h)[a]	Product		Yield[b] (%)
1		**2a**	1		**5a**	90
2		**2b**	1		**5b**	92
3		**2c**	1		**5c**	91
4		**2d**	1		**5d**	89
5		**2e**	1		**5e**	80
6		**2f**	2		**5f**	79
7		**2g**	3		**5g**	81
8		**2h**	1		**5h**	83

[a]Time required for the reaction of sulfamidates **2** with diselenide **3n** in the presence of rongalite **1**.
[b]Isolated yields after purification by column chromatography.

To extend the scope of this reaction further, we decided to study the reactivity of different cyclic sulfamidates **2** with diphenyl diselenide **3n** in the presence of **1**.
The reaction of sulfamidates **2a–2h** with diphenyl diselenide **3n** in the presence of rongalite **1** (rt, 1–3 h), resulted in the formation of the corresponding β-amino selenides **5a–5h** in good to excellent yields (Table 4). The sulfamidates **2a–2e** underwent facile ring opening with phenyl selenoate anion derived from diphenyl diselenide **3n** regioselectively at **C**-1 to give the desired products **5a–5e** respectively in excellent yields (Table 4, entries 1-5 and 8). Sterically crowded sulfamidates such as **2f, 2g** reacted slowly (2-3 h) to give the products **5f** and **5g** respectively in good yields (Table 4, entries 6–7). The Cbz-protected sulfamidate **2h** underwent ring opening smoothly in 1 h give the corresponding β-amino selenide **5h** in 83% yield.

Reaction of cyclic six membered sulfamidate 2i with diphenyl dichalcogenides (3a and 3n) in the presence of 1

An additional utility of this method was demonstrated in the reaction of six membered cyclic sulfamidate **2i** derived from 2,2-dimethylpropane-1,3-diol (Scheme 5). When the sulfamidate **2i** was treated with diphenyl disulfide **3a** and rongalite **1**, the reaction proceeded cleanly (DMF, rt, 1 h) to give the γ-amino sulfide **4u** in 85% yield (Scheme 5). In a similar fashion, when the reaction of **2i** was performed with diphenyl diselenide **3n** and rongalite **1,** it underwent facile ring opening to furnish γ-amino selenide **5i** in 81% yield (Scheme 5). This result indicates the potential utility of this method for the synthesis of a number of substituted γ-amino sulfides/selenides.



Scheme 5. Reaction of 6-membered cyclic sulfamidate **2i** with **3a** and **3n**

Conclusions

In this paper, we have reported an efficient, mild and general method for the synthesis of β and γ-amino sulfides/selenides *via* regioselective ring opening of cyclic sulfamidates with dichalcogenides in the presence of rongalite. The significance of the method is the use of inexpensive reagents and avoiding the use of free chalcogenols. The versatility of this reaction has been demonstrated by preparing a number of β-amino sulfides/selenides having different *N*-protecting groups.

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Notes and references

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Electronic Supplementary Information (ESI) available: [Experimental procedure, Characterization data, ^{1}H and ^{13}C NMR spectra of all the new compounds]. See DOI: 10.1039/b000000x/

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